Heart-Rate Complexity for Prediction of Prehospital Lifesaving Interventions in Trauma Patients

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Background: Traditional vital signs often fail to identify critically injured patients soon enough to permit timely intervention. To improve our ability to forecast the need for prehospital lifesaving interventions (LSIs), we applied heart-rate complexity (HRC) analysis to the electrocardiogram (ECG) of patients en route to trauma centers.

Methods: Analysis of ECG and clinical data from 374 patients en route by helicopter to three urban Level I trauma centers was conducted. Waveforms from 182 patients were excluded (because of ectopy, noise, or inadequate length). Of the remaining 192 patients, 54 received 66 LSIs in the field (LSI group): intubation (n = 52), cardiopulmonary resuscitation (n = 5), cricothyroidotomy (n = 2), and pneumothorax decompression (n = 7); 138 patients did not (non-LSI group). In the field, heart rate, blood pressure, and the Glasgow Coma Scale score (GCS_{TOTAL}) and its motor component (GCS_{MOTOR}) were recorded. ECG was recorded during flight. Ectopy-free, 800-beat sections of ECG were identified off-line and analyzed by HRC methods including Sample Entropy (SampEn) and Detrended Fluctuations Analysis (DFA).

Results: There was no difference between LSI and non-LSI patients in heart rate or blood pressure. SampEn was lower in LSI than in non-LSI (0.88 ± 0.03 vs. 1.11 ± 0.03), as was DFA (1.09 ± 0.05 vs. 1.33 ± 0.03) and GCS_{MOTOR} (3.4 ± 0.4 vs. 5.7 ± 0.1) (all $p < 0.0001$). By logistic regression, SampEn, DFA, and GCS_{MOTOR} were independently associated with LSIs (area under the receiver operating characteristic curve, 0.897).

Conclusions: Decreased HRC is associated with LSIs in prehospital trauma patients. HRC may be useful as a new vital sign for identification of the severely injured.

Key Words: Heart rate, Electrocardiography, Nonlinear dynamics, Spectrum analysis, Transportation of patients.

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Compensatory mechanisms tend to prevent early changes in traditional vital signs such as the blood pressure (BP) in trauma patients, and may camouflage the true severity of injury until those mechanisms are exhausted. Heart rate (HR), commonly assumed to increase in severely injured patients, often decreases. This may lead to under-triage, and thereby to increased mortality.[1] In one study, fully 23% of prehospital trauma patients with normal vital signs required a lifesaving intervention (LSI).[2] To address this problem, new vital signs that are more accurate than the traditional ones will be needed.[2,3]

The problem of accurate triage is most acutely felt on the battlefield. Errors in triage during combat may place not only the patient, but also the medic, other members of the unit, and the aeromedical evacuation crew at risk. Combat medics need the ability to identify those patients who require LSIs, such as endotracheal intubation, hemorrhage control, and decompression of tension pneumothorax. Holcomb et al.[4] showed that manually obtained vital signs like radial pulse character and motor examination can be used to triage prehospital trauma patients, and that standard electronic monitors add little to the physical examination. But in the combat environment, and in mass-casualty homeland defense situations, it may not be possible for medics to perform hands-on assessment of casualties without risking exposure to hostile fire or other hazards. The concept of "remote triage" has therefore been proposed for the battlefield and other austere environments as a method of performing casualty assessment via telemetry, using worn electrocardiographic (ECG) or other sensors.[5] Assuming that earlier intervention will lead to improved outcomes, a primary purpose of remote triage is to determine whether the casualty needs an LSI.

In pursuit of this goal of improved field diagnosis and triage, several methods have been used to extract additional information from the beat-to-beat variability present in the HR. One such heart-rate variability (HRV) method, frequency-domain analysis, quantifies the strength of the HR's periodic oscillations.[6] Several authors have found that this approach

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permits identification of critically ill or injured patients.[7,8] In particular, Cooke et al.[5,9] found that abnormal HRV characterized the prehospital HRs of lethally injured patients.

Heart-rate complexity (HRC) is a different approach to the analysis of the heart-rate time series. HRC is a family of methods that quantify the amount of irregularity or randomness in the signal; the degree of self-similarity or fractality of the signal; and the presence of short- and long-range correlations in the data. A variety of conditions, to include normal ageing, congestive heart failure, myocardial infarction, and hypovolemia have all been shown to result in a decrease in HRC of the HR signal.[10–13] Decreased HRC, as quantified by irregularity metrics Approximate Entropy (ApEn)[11] and Sample Entropy (SampEn),[14] has correlated well with severity of hypovolemia in several animal and human studies.[15–18] In prehospital trauma patients, Batchinsky et al.[15] showed those with lethal injuries are characterized by decreased ApEn and SampEn and, thus, a state of low HRC.

Despite these observations, no study to date has examined the utility of HRV and HRC, either individually or in combination, for assessment of the need to perform LSIs in trauma patients. In this study, we therefore sought to determine whether changes in multiple metrics from HRC and HRV are independently associated with the need to perform LSIs. We hypothesized that new vital signs derived from HRV and HRC analysis will separate patients who undergo LSIs from those who do not.

METHODS

This study consisted of waveform analysis and retrospective review of clinical data from prehospital trauma patients. Patients were identified for this study using the Trauma Vitals database developed by the U.S. Army Institute of Surgical Research (Fort Sam Houston, TX).[2] The database stores prehospital patient data from point of injury until arrival via the Houston Life Flight helicopter service at a Level I trauma center in Houston, TX (Memorial Hermann Hospital); or via the San Antonio Air Life Service at one of two Level I trauma centers in San Antonio, TX (University Hospital or Brooke Army Medical Center). A Pic 50 vital sign monitor (Welch Allyn, Skaneateles Falls, NY) as well as a standard run sheet were used for ECG and patient data collection, respectively. The study was approved by the Institutional Review Boards of all three institutions. Conventional vital signs, mechanism of injury (blunt or penetrating), field Glasgow Coma Scale score (GCS), Abbreviated Injury Scores, Injury Severity Score, age, sex, conventional vital signs, and in-hospital mortality were recorded. BPs were measured automatically by cuff using the vital signs monitor. The list of lifesaving interventions (LSIs) included the following: cardiopulmonary resuscitation, cricothyroidotomy, endotracheal intubation, needle decompression of the chest, pericardiocentesis, and cardioversion.[2] Only LSIs performed in the field were included in this study.

Continuous ECG waveforms were recorded at a sampling frequency of 375 Hz to a PMCIA card on the Pic 50 monitor. ECGs collected from 374 patients were screened for the study. Patients were excluded from the study if: (1) ECG of 800 R-to-R intervals (RRIs) in length was not available for analysis; (2) ectopic beats were present within the analyzed data segments; or (3) ECG quality was inadequate due to electromechanical noise or disruption of the signal or both. The earliest available 800-beat data sets were imported into WinCPRS software (Absolute Aliens Oy, Turku, Finland) and were analyzed as previously described.[16,19] The software automatically identified R waves, and generated the instantaneous RRI time series. Accurate R-wave identification was manually verified for all data sets.

Frequency-domain and complexity analyses were performed as previously described.[16] The frequency-domain variables included those derived by Fast-Fourier transform: the total power (TP, calculated over 0.003–0.4 Hz), low-frequency power (LF, 0.04–0.15 Hz), high-frequency power (HF, 0.15–0.4 Hz), and LF/HF and HF/LF ratios of the signal. They also included those provided by complex demodulation (CDM): the low-frequency (CDM LF) and high-frequency (CDM HF) amplitudes of signal oscillations. The complexity variables included measures of the irregularity of the signal (ApEn and SampEn), its self-similarity (Fractal Dimension by Dispersion Analysis, [FDDA]), its Similarity of Distribution (SOD), and short-term correlations in the signal by Detrended Fluctuation Analysis (DFA).

SAS version 9.1 (SAS Institute, Cary, NC) was used for statistical analysis. Normality of continuous variables was assessed with the Shapiro-Wilk test. Univariate analysis was performed using two-samples Student's *t* test or Mann-Whitney *U* test as appropriate for continuous variables, the Mann-Whitney *U* test for score variables, and χ^2 or Fisher's exact test for categorical variables. In addition, Pearson and Spearman correlation coefficients were calculated to determine relationships between variables.

Multiple logistic regressions with stepwise selection and likelihood ratio tests were performed to identify independent predictors of LSIs. We considered this to represent a diagnostic problem with two overlapping phases. In the first phase ("remote triage"), only data derived from the RRI time series and, thus, potentially available by remote telemetry, were considered. Under this hypothetical scenario a subject would be evaluated from a telemetrically acquired section of his or her ECG waveform. In the second phase ("prehospital care"), additional data available to the field medic, to include the GCS_{MOTOR} and the BP, were also considered. The Hosmer-Lemeshow goodness-of-fit test was used to estimate the regression model fit. Receiver operating characteristic curves were constructed to assess the diagnostic performance of predictive equations. Estimated odds ratios (ORs) and their 95% confidence intervals (CIs) were determined by the maximum likelihood method.

RESULTS

Data from 401 patients were screened for this study. Twenty-seven patients were excluded because of incomplete clinical records. Clinical data and ECG waveforms from 374 patients were present and were manually reviewed for this study. Waveforms from 182 patients were excluded from the study (104 due to multiple ectopic beats, 19 due to electromechanical noise, and 59 due to inadequate data set length). This resulted in a total of 192 patients available for analysis.

Of these 192 patients, 54 (28.1%) underwent a total of 66 LSIs (of the 209 patients who were excluded, 54 [25.8%] patients also had LSIs). LSIs in the 54 included patients were intubation (n = 52), cardiopulmonary resuscitation (n = 5), cricothyroidotomy (n = 2), and decompression of tension pneumothorax (n = 7). Patients in the LSI group were younger but did not differ from the non-LSI group with respect to other demographics, systolic arterial pressure, pulse pressure, shock index, HR, incident-to-hospital time, and amount of fluids infused (Table 1). Patients requiring LSIs had decreased mental status (lower GCS_{TOTAL} and GCS_{MOTOR} scores), and were more severely injured (higher Injury Severity Score). However, Abbreviated Injury $Score_{HEAD}$ was not different. There was a significant difference in mortality between the groups: 14.8% in the LSI group (8 of 54 died) and 2.2% in the non-LSI group (3 of 138 died), $p = 0.0020$ (Table 1).

As measured by frequency-domain methods (Table 2), LSI patients were significantly different from non-LSI patients on several measures. These included decreased power (TP, LF, HF) and amplitude (CDM LF, CDM HF) of the RRI time series (Table 2).

Complexity measures, to include ApEn, SampEn, FDDA, and DFA, were all lower in the LSI group than in the non-LSI group. SOD was higher in LSI patients, which is also consistent with decreased complexity (Table 3).

Independent Predictors of the Need for Lifesaving Intervention

As explained above, construction of logistic regression models for prediction of LSIs progressed through two phases. For the remote triage phase, only RRI-derived variables were considered. This model (model 1) is described by the following equation:

$p(LSI) = e^k/(1 + e^k)$, where $k = 3.616 - 2.510 * (SampEn) - 1.679 * (DFA)$.

This model indicates that a higher SampEn, or a higher DFA, each independently predict a decreased likelihood of undergoing an LSI. ORs and their 95% CI for this model were as follows: OR (SampEn) = 0.081 (CI = 0.026, 0.251); OR (DFA) = 0.186 (CI = 0.081, 0.428). The area under the receiver operating characteristic curve (AUC) was 0.760 (CI = 0.682, 0.838); see Figure 1.

For the second or "prehospital care" phase, the following model (model 2) was generated based on GCS_{MOTOR} alone:

Table 1 Demographics, Conventional Vital Signs, and Injury Scores

Variable	Non-LSI (n = 138)	LSI (n = 54)	p
Age (yr)	38.0 ± 1.1	33.9 ± 14.7	0.0252
Sex (male)	95 (68.8%)	42 (77.8%)*	0.1684
MOI (blunt)	116 (84.1%)†	48 (88.9%)	0.8791
HR	99.17 ± 2.11	108.32 ± 4.88	0.0827
SAP	124.60 ± 2.16	119.48 ± 4.68	0.2871
PP	40.0 ± 1.3	41.3 ± 2.0	0.332
SI	0.84 ± 0.03	0.92 ± 0.05	0.119
GCSTOTAL	13.97 ± 0.22	8.10 ± 0.80	<0.0001
GCSMOTOR	5.73 ± 0.08	3.41 ± 0.35	<0.0001
AISHEAD	2.88 ± 0.20	3.41 ± 0.21	0.1213
ISS	13.22 ± 0.77	18.54 ± 1.44	0.0005
Incident to hospital (min)	69.5 ± 2.4	72.4 ± 2.9	0.2341
Fluids (mL)	668.09 ± 64.11	744.63 ± 137.11	0.6585
Mortality	3 (2.2%)	8 (14.8%)	0.0020

* Sex of one patient not recorded.

† Mechanism not recorded in six patients. Data are means ± SEM.

MOI, mechanism of injury (number and percentage of blunt injuries); SAP, systolic arterial pressure; PP, pulse pressure (SAP—diastolic blood pressure); SI, shock index (HR/SAP); GCSTOTAL, field Glasgow Coma Score total; GCSMOTOR, field Glasgow Coma Score motor; AISHEAD, Abbreviated Injury Score for the head; ISS, Injury Severity Score.

Table 2 Heart-Rate Variability (Frequency-Domain) Results

Variable	Non-LSI (n = 138)	LSI (n = 54)	p
TP	873.74 ± 107.25	244.44 ± 49.43	<0.0001
LF	233.56 ± 27.29	49.27 ± 17.07	<0.0001
HF	66.16 ± 14.12	17.85 ± 7.39	<0.0001
LF/HF	5.59 ± 0.42	5.80 ± 7.66	0.0077
HF/LF	0.25 ± 0.03	0.41 ± 0.07	0.1351
CDM LF	14.49 ± 0.91	5.19 ± 0.88	<0.0001
CDM HF	6.64 ± 0.57	2.93 ± 0.53	<0.0001
CDM LF/HF	2.46 ± 0.10	1.92 ± 0.20	<0.0001

TP, total R-to-R interval spectral power (0.003–0.4 Hz); LF, RRI spectral power at the low frequency (0.04–0.15 Hz); HF, RRI spectral power at the high frequency (0.15–0.4); LF/HF, the ratio of LF to HF; HF/LF, the ratio of the HF to LF; CDM LF, amplitude of the LF oscillations by complex demodulation; CDM HF, amplitude of the HF oscillations. Data are means ± SEM.

Table 3 Heart-Rate Complexity Results

Variable	Non-LSI (n = 138)	LSI (n = 54)	p
ApEn	1.09 ± 0.02	0.91 ± 0.04	0.0001
SampEn	1.11 ± 0.03	0.88 ± 0.03	<0.0001
FDDA	1.12 ± 0.01	1.07 ± 0.01	<0.0001
DFA	1.33 ± 0.03	1.09 ± 0.05	<0.0001
SOD	0.15 ± 0.00	0.20 ± 0.01	<0.0001

ApEn, approximate entropy; SampEn, sample entropy; FDDA, fractal dimension by dispersion analysis; DFA, short-term correlations within the RRI by Detrended Fluctuations Analysis; SOD, similarity of distribution. Data are means ± SEM.

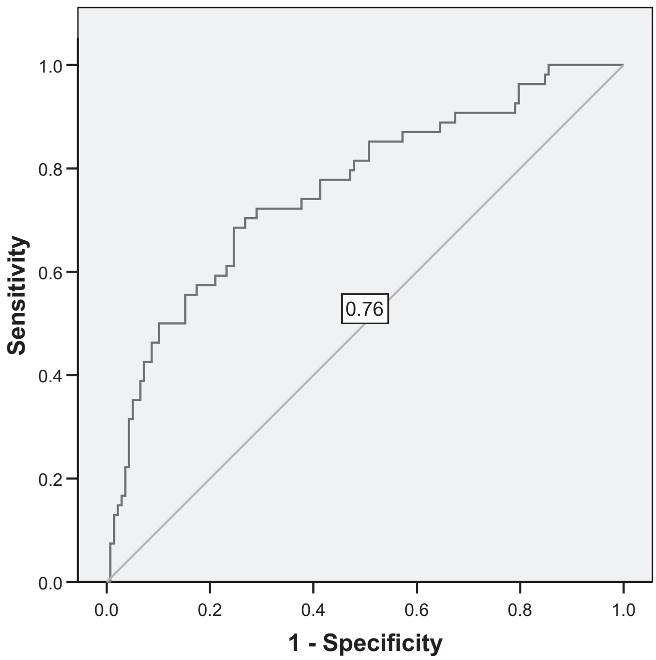

Fig. 1. *Receiver operating characteristic (ROC) curve for model derived by logistic regression for prediction of lifesaving interventions (LSIs) using ECG variables alone. SampEn and DFA were independently associated with LSIs. Area under the curve (AUC) = 0.76.*

$p(LSI) = e^k/(1 + e^k)$, where $k = 3.021 - 0.823 * (GCS_{MOTOR})$.

This model indicates that a higher GCS_{MOTOR} is associated with a decreased likelihood of an LSI. OR (GCS_{MOTOR}) = 0.439 (CI = 0.330, 0.585); AUC = 0.800 (CI = 0.708, 0.892); see Figure 2.

Finally, the RRI- and physical-examination-based variables were considered together, and the following model (model 3) was generated based on SampEn, DFA, and GCS_{MOTOR}:

$p(LSI) = e^k/(1 + e^k)$, where $k = 7.751 - 2.569 * (SampEn) - 1.952 * (DFA) - 0.801 * (GCS_{MOTOR})$.

OR (SampEn) = 0.077 (CI = 0.016, 0.362); OR (DFA) = 0.142 (CI = 0.045, 0.445); OR(GCS_{MOTOR}) = 0.449 (CI = 0.332, 0.607). AUC = 0.897 (CI = 0.839, 0.956); Figure 3. For all the above models, the Hosmer and Lemeshow goodness-of-fit test revealed no significant departure from good fit ($p > 0.2$).

DISCUSSION

This report is the first to employ comprehensive analysis of HRV by both complexity and frequency-domain methods for prediction of LSIs in prehospital trauma patients. The major findings of this study are that patients who received LSIs had (1) lower HRC by multiple metrics, including SampEn, Detrended Fluctuations Analysis (DFA), and SOD; (2) abnormal frequency-domain measures of HRV; (3) lower GCS_{MOTOR} at the scene; and (4) more severe injuries and higher mortality. SampEn, DFA, and GCS_{MOTOR} were independent predictors of LSI in a final model with an AUC of 0.897, whereas conventional vital signs such as the HR and BP were not associated with performance of LSIs.

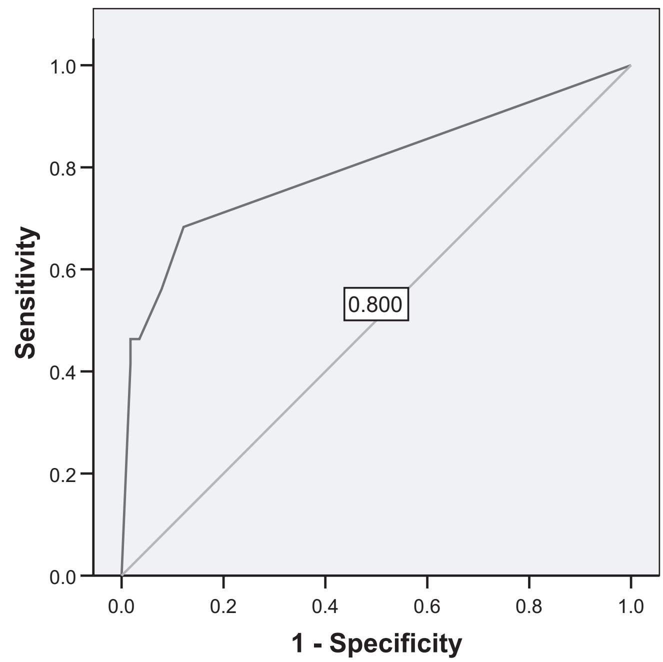

Fig. 2. *ROC curve for model derived by logistic regression for prediction of LSIs using the motor component of the Glasgow Coma Scale score (GCS_{MOTOR}) alone. AUC = 0.80.*

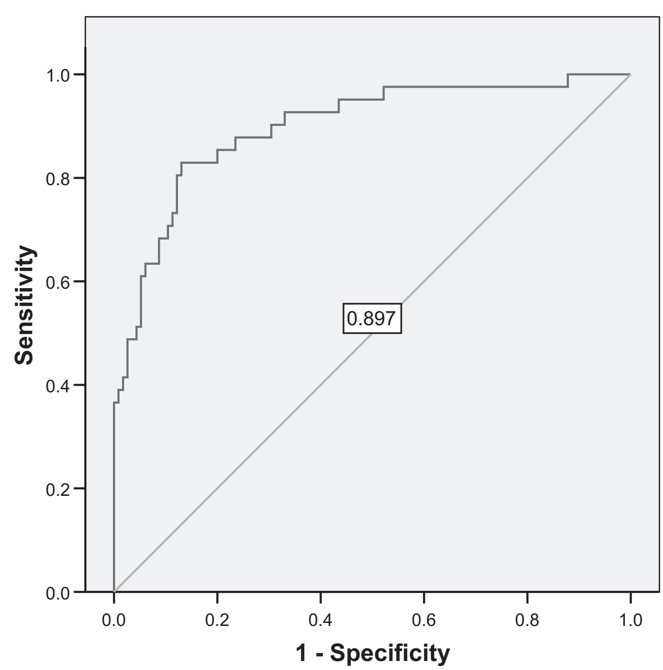

Fig. 3. *ROC curve for model derived by logistic regression for prediction of LSIs using ECG-derived variables (SampEn and DFA) and GCS_{MOTOR} together. AUC = 0.897.*

The complexity of a signal like the HR can be measured by a variety of methods, and our finding of decreased HRC in

LSI patients is solidified by the fact that several computationally distinct methods produced similar results. The entropy methods (ApEn[11,20] and SampEn[14]) quantify the probability of a repetitive pattern in the RRI. If the next pattern can be predicted from the previous section of the signal, the signal is deemed regular, low in entropy, and less complex. Conditions in which the amount of regulatory feedback is reduced may cause a decrease in RRI entropy.[20] In the present study, patients in need of LSI were characterized by lower levels of both ApEn and SampEn. This finding is similar to our previous work in which nonsurviving trauma patients showed lower ApEn and SampEn than survivors.[15] Low ApEn and SampEn values were also identified in severely burned patients shortly after arrival to the burn center; resuscitation increased entropy in those patients.[21] The latter study suggests that assessment of HRC via entropy methods can be used not only to identify more severely injured patients that are more likely to need an LSI but also to monitor the response to such interventions such as, for example, resuscitation. Others have noted decreased entropy in patients who develop atrial fibrillation after coronary artery bypass grafting,[22] and in patients with myocardial ischemia.[23] Taken together, these reports suggest that decreased HRC may be a common feature seen in many types of critical illness and may be a suitable new vital sign for identification of the severely injured.

SampEn and ApEn are very similar computationally, but SampEn has the advantage of being relatively unaffected by a decrease in the number of beats (RRIs) in the data set, down to a data set size of about 100 beats.[14,21] ApEn, on the other hand, is preferably computed on data sets of 800 beats or more.[19] Thus, SampEn may be more useful than ApEn for emergency triage situations when only short segments of ECG data are available and trending of data are not feasible.

Another method of HRC analysis quantifies the degree to which the RRI time series resembles a fractal, i.e., possesses self-similarity at multiple scales. This fractal characteristic is a normal property of the RRI in healthy individuals.[12] The traditional approach to fractal analysis is represented by the FDDA. FDDA has values between 1 (constant signal) and 1.5 (maximally fractal or random signal). Our results show that the subjects with LSIs had a more pronounced breakdown in fractal properties of their RRI time series than the injured patients that did not undergo LSIs. These findings are in line with our previous work that identified decreased FDDA values in lethally injured trauma patients.[15]

DFA is another method of measuring fractal processes that quantifies correlations within the data over time.[24] The DFA concept means that fluctuations in HR in normal people are affected not only by the most recent value but also by more remote events—a type of "memory effect."[25] In this study, we used DFA to assess the short-term correlations in the RRI signal, and found it to be significantly lower in the LSI group. This is consistent with our previous study in prehospital trauma patients, in which nonsurvivors had a lower short-term exponent by DFA than less injured nonsurvivors.[15] Other authors have found decreased DFA in patients with myocardial infarction and in patients who go on to develop atrial fibrillation.[26–28] Our findings are, therefore, consistent with the literature indicating an association between decreased short-term RRI fractal scaling and critical illness.

SOD is another complexity method that explores the probability of similar RRI signal-amplitude distributions as a function of time.[29] SOD was higher in the LSI group, reflecting greater regularity of signal distribution. This result is consistent with our findings in a different cohort of prehospital trauma patients, in which increased SOD was associated with more severe injuries and death.[15]

Whereas complexity methods quantify the informational content in the signal structure, frequency-domain methods such as fast-Fourier transform measure the strength of regular oscillations in the signal. Oscillations that occur at the same frequency as the respiratory rate (respiratory sinus arrhythmia) are quantified by the HF power. Those that occur at a slower rate (about once every 10 second) are quantified by the LF power. These variables have been shown (e.g., by autonomic blockade studies) to be affected by the activity in the autonomic nervous system. That is, HF relates to vagal cardiac control and LF to both vagal and sympathetic cardiac control. The ratio of these numbers (LF/HF) has been proposed as an index of the relative amounts of sympathetic and vagal nerve inputs to heart-rate control ("sympatho-vagal balance"). The converse can be expressed as the HF/LF ratio.[6,30,31] The TP is a measure of overall variability.

Hypovolemia has been associated with alterations in these ratios that have been interpreted as compensatory increases in sympatho-vagal balance, indicative of sympathetic activation and vagal withdrawal.[32–34] On the other hand, sympathetic failure, manifested by a decrease in sympatho-vagal balance, was predictive of death in intensive care unit patients[7,35] and in prehospital trauma patients.[5,9] In the current study, however, we did not find that this relative deficiency in sympathetic activation also relates to the need for LSIs.

Fast-Fourier transform analysis quantifies the power (area under the curve of the power spectrum) of the RRI signal. By contrast, the method of CDM provides continuous assessment of the amplitude of HF and LF fluctuations in the RRI.[21,36] As measured by CDM, the amplitudes of LF and HF oscillations were both lower in LSI group, as was the CDM LF/HF ratio. Thus, severely injured patients who eventually received LSIs were characterized by a state of depressed HRV as evident from decreased power and amplitude of methodologically different HRV metrics.

By multivariate analysis, SampEn, DFA, and GCS_{MOTOR} were all independently associated with performance of LSIs. Inclusion of both ECG-derived variables in the model suggests that SampEn and DFA may provide complementary information about the patient's condition and could be incor-

porated into a decision-support device for wear by soldiers and other personnel operating in austere environments, facilitating remote monitoring and triage.

Perspectives

The present study involved manual review of ECGs, a process which is fairly easily learned, but too time-consuming for routine clinical use in trauma patients. To address this limitation, we have developed and are testing algorithms that automatically calculate several of the variables of interest in real time. Second, we excluded a large percentage (45%) of study patients because of excessive noise, ectopy, or inadequate length of the ECG. These limitations could be mitigated by (1) incorporation of automated ECG filtering, R-wave detection, and quality assessment tools (2) development of techniques that are not hampered by ectopic beats; and (3) use of algorithms which provide meaningful information with smaller data sets. Until these problems are overcome, the clinical utility of these findings will be somewhat limited.

It is also important to point out that this study took place in urban U.S. trauma systems, that most of the patients had blunt trauma, and that the LSIs were primarily related to airway management. Ongoing studies in combat casualties will address the applicability of the HRC methods to patients with severe hemorrhage, who require treatment e.g., with a blood transfusion, a tourniquet, or a hemostatic dressing.

To understand more fully the utility of these new vital signs, they should be incorporated into automated algorithms installed on commercial monitors and evaluated in larger multicenter trials in diverse cohorts of critically ill patients. These studies should include validation of the models in data sets and not used for model development. Also, research needs to be completed to determine the effect of physical exertion, heat injury, psychological stress, medications, co-morbidities, and other potentially confounding but clinically relevant states on these metrics.

CONCLUSION

In conclusion, 800-beat sections of ECG data from prehospital trauma patients were analyzed by frequency-domain and complexity methods. We found that decreases in SampEn and short-term correlations by DFA, along with the motor component of the GCS score, were independently associated with the performance of LSIs. These "new vital signs" may improve clinical care by helping providers to identify those patients who need an LSI. Further work is needed to automate the waveform analysis process, and to decrease the number of ECGs rejected because of ectopy, noise, or short datasets.

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